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Attention-deficit hyperactivity disorder (ADHD) as a pyridoxine-dependent condition: Urinary diagnostic biomarkers

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In 70s Coleman et al. published several articles on the effect of pyridoxine hydrochloride (vitamin B6; 30 mg/kg) in patients with ADHD. The approach however did not get any serious attention. Shown recently mutual interconnections between ADHD and epilepsy (co-morbidity between the diseases; ADHD as a risk factor for epilepsy; epilepsy as a risk factor for ADHD), as well as our data, elucidating epilepsy as an inborn error of pyridoxine metabolism (Dolina et al, 2012) enable to use similar approaches for both diseases. The urinary parameters of pyridoxal phosphate (PLP)-dependent tryptophan (TRP) degradation were detected in ADHD children. The level of TRP, concentrations of compounds formed or metabolized by Kynurenine (KYN) pathway, the ratios between some of them, and also the level of 4-pyridoxic acid (4-PA, the end product of pyridoxine metabolism) were HPLC detected in children with ADHD and healthy controls. Comparing to healthy controls, threefold increase in the level of TRP, more than twofold increase in the level of KYN and toxic 3-hydroxykynurenine (3-HOKYN), fourfold reduction in the ratio of 3-hydroxyanthranilic acid to 3-hydroxykynurenine (3-HOAA/ 3-HOKYN), reflecting activity of kynureninase (the enzyme critically sensitive to PLP supply), and sharply diminished level of Indoxyl sulfate (IND), were found in ADHD children. These data along with low 4-PA/TRP, IND/TRP and IND/KYN ratios, low monoamines (catecholamines and serotonin) and glutamate/ GABA imbalance -support the hypothesis of strikingly impaired activity of pyridoxine-dependent enzymes in ADHD patients.

Treatment with Ritalin did not change the general pattern of TRP degradation, but yet created a kind of balance between detected metabolites. TRP level in treated patients appeared to be twice as high as in healthy controls. The concentration of neurotoxic 3-HOKYN was reduced to the control level, thereby significantly increasing the 3-HOAA/3-HOKYN ratio. However, the 4PA/TRP ratio as well as the level of IND remained low, pointing to the value of IND/TRP and IND/KYN ratios as diagnostic markers of the disease.

Almost identical parameters of TRP degradation in untreated ADHD and epileptic patients suggest that inborn disorders of vitamin B6 metabolism are the common biochemical background of both diseases. The disordered activity of PLP - dependent enzymes evidently forms a diversity of neurotransmitter disturbances, characteristic of ADHD: low monoamines and disordered amino acid metabolism. If vitamin B6 disorders are indeed the core biochemical disturbances inherent in ADHD, then the long-term Pyridoxine treatment represents pathogenetically based replacement therapy for the disease. According to our data, the doses three times less than those, suggested by Coleman group, are effective: 7-10 mg/kg of pyridoxine hydrochloride daily (up to100 mg /day in children of 4-8 years; 200 mg/day in adolescents) change completely pattern of behavior, causing no side effects for years. Pyridoxine administration will probably change the level of each relevant biomarker, turning them to be dynamic indicators of treatment effect.

Keywords: Attention deficit hyperactivity disorder, tryptophan degradation, kynurenines, Vitamin B6-dependent enzymes.

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